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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/723,423
Filing Date: November 26, 2003
Appellant(s): JENSEN ET AL.

Robert J. Harris
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7-22-10 appealing from the Office action mailed 6-24-09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 54-58. Claims 1-53 and 59-63 have been cancelled by applicant.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner:

1) 112, second paragraph rejection

2) 103 rejection over Lopez-Berestein, Allen (BBA), Fujii (5,328,678), and O'Rear (5,503,850) individually or in combination and Hersch; OR Hersch, Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination further in view of Abra (5,945,122) since appellant has cancelled the claims relevant thereto.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5,759,571	HERSCH	6-1998
5,328,678	FUJII	7-1994
5,503,850	O'REAR	4-1996
5,032,404	LOPEZ-BERESTEIN	7-1991
5,869,092	HAYES	2-1999
4,999,199	ANAISSIE	3-1991

Allen, T. M. et al, "Serum-induced Leakage of Liposome Contents", Biochimica Biophysica Acta, vol. 597, (1980), pp. 418-426.

(9) Grounds of Rejection

1. Claims 54-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hersch (5,759,571) by itself or in combination with Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination.

According to instant claims, the liposomes contain different phosphatidylcholines and cholesterol and some liposomes contain even the negatively charged lipid, DSPG

(distearoyl phosphatidylglycerol). The amounts of cholesterol vary from approximately 33 % to 25 %.

Hersch discloses liposomes containing amino glycoside, amikacin. The liposomal formulations contain various claimed neutral phospholipids, hydrogenated soy phosphatidylcholine (HSPC, DMPC, DSPC, DPPC, anionic phospholipids and cholesterol, in particular HSPC and DSPG and cholesterol. According to Hersch, the preferred ratio of HSPC: cholesterol and DSPG is 2:1:0.1, although in claim 1 Hersch does not indicate any specific amounts. Further according to Hersch, DSPG can be varied from 0 to 20 % (abstract; col. 3, line 65 through col. 6, line 63; Examples and claims. The liposomal sizes are less than 100 nm. Hersch does not teach all of the claimed phosphatidylcholine and all of the ratios with respect to the phospholipids and cholesterol. However, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the lipids, cholesterol and drug from the guidance provided by Hersch to obtain the best possible results.

Allen teaches that the presence of serum significantly increased liposome leakage and the incorporation of increasing molar ratios of cholesterol into liposomes was required to reduce the leakage of calcein (active agent) from the liposomes incubated with buffer and with serum (Summary, Tables and Figures). This implies that the active agent from liposomes without cholesterol will leak and release the active agent quickly as opposed to liposomes with increasing amounts of cholesterol.

Fujii teaches that sterols such as cholesterol help stabilize the bilayer toward leakage and destruction in the plasma (col. 3, lines 5-10).

O'Rear teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by appropriate manipulation of the liposomal membrane fluidity and composition. O'Rear further teaches that in the absence of cholesterol, liposomes may leak substantially when introduced intravenously and that cholesterol alters the mechanical and structural properties of the phospholipid bilayer of the liposome to cause variable permeability and fragility (col. 3, line 58 through col. 4, line 5).

To vary the cholesterol amounts in Hersch with respect to other phospholipids would have been obvious to one of ordinary skill in the art depending upon the type of release of the active agent (quicker or slower release of the active agent in the blood) based on the teachings of Allen, Fujii and O'Rear. Thus, the selection of appropriate phospholipid and manipulating the amounts of cholesterol would have been obvious based on the teachings of O'Rear. Although Hersch does not specifically teach the claimed neutral phospholipids (DEPC and DOPC), on col. 5, lines 56-66 he teaches that the preferred neutral phospholipids have a chain length of 16 to 18 carbon atoms and other suitable phosphatidylcholines include those obtained from egg or plant sources and those that are partially or wholly synthetic; Therefore, it would have been obvious to one of ordinary skill in the art to choose the appropriate phosphatidylcholine with a reasonable expectation of success.

2. Claims 54-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopez-Berestein (5,032,404) by itself or in combination with Allen (BBA), Fujii (5,328,678), and O'Rear (5,503,850) individually or in combination, further in view of Hersch (5,759,571).

Lopez-Berestein discloses liposomes containing polyene antibiotics. The liposomal formulations contain various claimed phospholipids and cholesterol. The phospholipids include DSPC, DEPC, DMPC, DOPC and phosphatidylglycerols. The liposomes are either unilamellar or multilamellar. The liposomes are administered parenterally. The lipid-drug ratios and the lipid-cholesterol ratios disclosed by Lopez-Berestein fall within the claimed ratios (abstract; col. 7, line 49 through col. 8, line 13; col. 8, lines 34-66; col. 9, lines 15-47; Table 5; Examples, in particular Example 3, 15 and claims).. According to Lopez-Berestein the compositions include Cholesterol in concentrations from 10 to 75 weight percentages. The amounts of phospholipids (10 mg) and cholesterol (3, 2 and 1 mg) when expressed in molar amounts appear to be closer to the 4:1:0.1 ratios of HSPC, cholesterol and DSPG in instant claim 1. In view of Lopez-Bernstein's teachings of the claimed phospholipids and the suggestion that the amounts of cholesterol can be varied from 10 to 75 weight percentages, it would have been obvious to one of ordinary skill in the art to select a phospholipid and vary the amount of cholesterol from the teachings of Lopez-Berestein with the expectation of obtaining the best possible results. Although Lopez-Berestein in examples uses DMPG, in view of his generic teachings of the use of phosphatidylglycerols, one would be

motivated to use a specific phosphatidylglycerol such as DSPG with a reasonable expectation of success.

Allen teaches that the presence of serum significantly increased liposome leakage and the incorporation of increasing molar ratios of cholesterol into liposomes was required to reduce the leakage of calcein (active agent) from the liposomes incubated with buffer and with serum (Summary, Tables and Figures). This implies that the active agent from liposomes without cholesterol will leak and release the active agent quickly as opposed to liposomes with increasing amounts of cholesterol.

Fujii teaches that sterols such as cholesterol help stabilize the bilayer toward leakage and destruction in the plasma (col. 3, lines 5-10).

O'Rear teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by appropriate manipulation of the liposomal membrane fluidity and composition. O'Rear further teaches that in the absence of cholesterol, liposomes may leak substantially when introduced intravenously and that cholesterol alters the mechanical and structural properties of the phospholipid bilayer of the liposome to cause variable permeability and fragility (col. 3, line 58 through col. 4, line 5).

Assuming that the cholesterol amounts in Lopez-Berestein are different from instant amounts, it would have been obvious to one of ordinary skill in the art to decrease its amounts if quicker release of the active agent in the blood is desired based on the teachings of Allen, Fujii and O'Rear. Thus, the selection of appropriate

phospholipid and manipulating the amounts of cholesterol would have been obvious based on the teachings of O'Rear. Although, the amounts of phosphatidylglycerol in Lopez-Berestein are higher, one of ordinary skill in the art would be motivated to change the amounts in view of Hersch's teachings that the amounts of phosphatidylglycerol can be varied from 0 to 20 %. As pointed out above, Lopez-Berestein teaches generic phosphatidylglycerol, but not specific species such as distearoylphosphatidylglycerol (DSPG). As also pointed out above, Hersch teaches DSPG as a preferred phospholipid in combination with phosphatidylcholine. Therefore, it would have been obvious to one of ordinary skill in the art to use DSPG taught by Hersch as the specific PG in Lopez-Berestein with a reasonable expectation of success. Alternately, to include a phosphatidylcholine such as DEPC in Hersch would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Lopez-Berestein teaches that this phosphatidylcholine could be used in combination with phosphatidylglycerol.

3. Claims 55-56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayes (5,869,092) by itself or in combination with Hersch (5,759,571), Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination.

According to instant claim 25, the liposomes comprise DEPC and cholesterol in a ratio of about 2:1.

Hayes teaches liposomal compositions containing dielaidoylphosphatidylcholine or dimyristoylphosphatidylcholine. According to Hayes, the commonly used lipid

component is phosphatidylcholine and the phosphatidylcholines to which a variety of acyl chain groups of varying chain length and degree of saturation have been bonded are commercially available or may be isolated or synthesized by well-known techniques and that the more common phosphatidylcholines are those containing saturated fatty acids with carbon chain lengths in the range of C 14 to C 22, although phosphatidylcholines from mono- or di-unsaturated fatty acids and from mixtures of saturated and unsaturated are of use as well. The other phospholipids which could be used in combination include phosphatidylglycerols (abstract, column 7, line 53 through col. 8, line 9; col. 9, line 36; examples 2 and 3). According to Hayes cholesterol can be present in amounts from 0.1 to 1.0 mole ratio (col. 8, lines 4-9). The liposomes encapsulate either a lipophilic drug or a hydrophilic drug (col. 8, lines 40-56). According to Hayes, the phospholipid can be either DEPC or DMPC (claim 12). . Further according to Hayes, the liposomes can further include negatively charged phospholipids and the choice of the lipid is generally based on such factors as the desired size and stability of the resulting liposomes in the blood stream or other intended mode of administration (col. 7, lines 45-52). The inclusion of cholesterol in instant amounts in DEPC liposomes would have been obvious to one of ordinary skill in the art since Hayes is suggestive of the inclusion of cholesterol from 0.1 to 1 mole ratios with the phospholipid. The inclusion of a negatively charged phospholipid such as phosphatidylglycerol (DSPG) would have been obvious to one of ordinary skill in the art since Hayes is suggestive of such an inclusion. Although Hayes does not teach instant amounts of phosphatidylglycerol, in

the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts to obtain the best possible results.

Hersch discloses liposomes containing amino glycoside, amikacin. The liposomal formulations contain various claimed neutral phospholipids DMPC, DSPC, DPPC, anionic phospholipids and cholesterol, in particular HSPC, cholesterol and DSPG in a ratio of 2:1: 01. The lipid-drug ratios fall within the claimed amounts. The liposomal sizes are less than 100 nm. The method disclosed includes IV injection into mice. The method also includes patients (humans) (abstract; col. 3, line 65 through col. 6, line 63; Examples and claims).

Allen teaches that the presence of serum significantly increased liposome leakage and the incorporation of increasing molar ratios of cholesterol into liposomes was required to reduce the leakage of calcein (active agent) from the liposomes incubated with buffer and with serum (Summary, Tables and Figures). This implies that the active agent from liposomes without cholesterol will leak and release the active agent quickly as opposed to liposomes with increasing amounts of cholesterol.

Fujii teaches that sterols such as cholesterol help stabilize the bilayer toward leakage and destruction in the plasma (col. 3, lines 5-10).

O'Rear teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by appropriate manipulation of the liposomal membrane fluidity and composition. O'Rear further teaches that in the absence of cholesterol, liposomes may leak substantially

when introduced intravenously and that cholesterol alters the mechanical and structural properties of the phospholipid bilayer of the liposome to cause variable permeability and fragility (col. 3, line 58 through col. 4, line 5).

Assuming that the cholesterol amounts in Hayes with respect to other phospholipids are different from instant amounts, it would have been obvious to one of ordinary skill in the art to decrease its amounts based on the teachings of Hersch and if quicker release of the active agent in the blood is desired, based on the teachings of Allen, Fujii and O'Rear. Thus, the selection of appropriate phospholipid and manipulating the amounts of cholesterol would have been obvious based on the teachings of O'Rear.

4. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hayes (5,869,092) alone or in combination with Hersch (5,759,571), Allen (BBA), Fujii (5,328,678), O'Rear (5,503,850) individually or in combination as set forth above, further in view of Anaissie (4,999,199).

The teachings of Hayes and other references have been discussed above. What is lacking in Hayes is the teaching that the phospholipid used in the liposome formation be DOPC.

Anaissie while disclosing liposomal formulations containing polyene antibiotics teaches that either DEPC or DOPC can be used (abstract, col. 7, lines 20-28).

The use of DOPC instead of DEPC taught by Hayes would have been obvious to one of ordinary skill in the art since Anaissie teaches the equivalency between these two phospholipids in liposomal formulations.

(10) Response to Argument

REJECTION 1:

Appellant's arguments have been fully considered, but are not found to be persuasive. Appellant argues that Hersch at col. 6, lines 11-17 recites liposomes with a preferred ratio of HSPC: cholesterol: DSPG of about 2:1:0.1 and the drug to total lipid ratio of about 1:4 and that the office action has provided no text reference or knowledge why the above ratio suggest an HSPC: cholesterol: DSPG ratio of 4:1:0.1 as recited in claim 24. This argument is not persuasive since at the same location, Hersch teaches "Other preferred formulations include DSPG in a molar amount ***of 0*** to 20 % and most preferably in a molar amount ***of less than 5*** %. Furthermore, from the secondary references, it is evident that one can change the amounts of cholesterol. If the amounts of the cholesterol and the negatively charged lipids are changed, it would be obvious to one of ordinary skill in the art that the ratios of the phospholipid to the altered values of cholesterol and the negatively charged lipid would also change. Appellant further argues that the Hersch formulation of 2:1:0.1 would have a long half life as compared to the presently claimed ratio that has an intermediate release value which imparts an unexpected result to the present claims as compared to what is taught by Hersch. This

argument is not persuasive. First of all without a comparison with Hersch formulations experimentally, this statement is deemed to be speculative. Secondly, it is clearly evident from the secondary references that the release properties are modified by the amount of cholesterol in the liposomes and therefore, one of ordinary skill in the art would adjust the ratios to obtain the desired release rates for the drug. It is unclear to the examiner why the results are unexpected.

Appellant argues that Allen, Fujii and O'Rear references discuss liposomes that include cholesterol, but do not speak to the differences between the ratios of phosphatidylglycerol lipids to phosphatidylcholine lipids as discussed above and therefore, do not remedy the deficiencies of Hersch. Further according to appellant, the liposomes of Allen, Fujii and O'Rear are different from instant liposomes. These arguments are not persuasive since from the teachings of the secondary references it is evident that cholesterol has the ability to provide flexibility to the bilayer membrane of the liposomes and change the release rates and this function of cholesterol would be the same irrespective of the nature of the Phospholipid used in the formation of the bilayer membrane of the liposome.

With regard to claim 55, appellant argues that claim 55 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises dieleidoyl phosphatidylcholine and cholesterol in a ratio of 2:1 and Hersch does not teach or suggest a formation of DEPC: cholesterol liposome.

With regard to claim 56 appellant argues that claim 56 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises

dieleidoyl phosphatidylcholine: cholesterol: DSPG in a ratio of 2:1:01 and Hersch and the secondary references do not teach this phosphatidylcholine.

With regard to claim 57, appellant argues that claim 57 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises dioleoyl phosphatidylcholine: cholesterol in a ratio of about 2:1 and Hersch or the secondary references do not teach or suggest the features of claim 57.

With regard to claim 58, appellant argues that claim 57 is directed to a formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises dimyristoyl phosphatidylcholine: cholesterol: DSPG in a ratio of about 2:1:0.1 and Hersch and the secondary references do not teach or suggest the features of claim 58.

These arguments are not persuasive since Hersch as pointed out above does not specifically teach the claimed neutral phospholipids (DEPC and DOPC), on col. 5, lines 56-66 he teaches that the preferred neutral phospholipids have a chain length of 16 to 18 carbon atoms and other suitable phosphatidylcholines include those obtained from egg or plant sources and those that are partially or wholly synthetic; With these teachings and with the teachings of 2:1 ratio of phosphatidylcholine: cholesterol and 0 to 20 % of negatively charged lipid, it would have been obvious to one of ordinary skill in the art to choose the appropriate phosphatidylcholine including the claimed specific phosphatidylcholines with a reasonable expectation of success.

REJECTION 2:

Appellant's arguments have been fully considered, but are not persuasive. Appellant argues that Lopez-Berestein describes a system wherein hydrophobic therapeutic agent is trapped in the lipid bilayer of the liposome, rather than being located in the hydrophilic interior of the liposome and in contract, the instant claims recite a lipophobic therapeutic agent. This argument is not persuasive since Lopez-Berestein on col. 7, lines 59-61 clearly teaches that the polyene macrolide compound may be a part of the phospholipid lamellae, part of the encapsulated intraliposomal fluid or both. It is well-known in the art of liposomes that the intraliposomal fluid is an aqueous fluid and that water soluble compounds compartmentalize within the aqueous interior. Lopez-Berestein thus, is applicable to both water soluble as well as lipophilic compounds though Lopez-Berestein exemplifies only with lipophilic compounds. Appellant has not shown any criticality of the applicability of the liposomal system only the water soluble compounds. Appellant argues that the liposomes of Lopez-Berestein are not formulated from HSPC: cholesterol: DSPG as recited in claim 54. This argument is not persuasive since Lopez-Berestein teaches generic phosphatidylcholine and the specific hydrogenated soy phosphatidylcholine is taught by Hersch. With regard to the ratios, the examiner has already calculated the ratios in terms of mole amounts based on the mg amounts taught by Lopez-Berestein and if different, it is deemed obvious to one of ordinary skill in the art to vary the ratios to obtain the best possible results.

Appellant's arguments that Hersch, Allen, Fujii and O'Rear neither individually nor in combination with Lopez-Berestein remedy the deficiencies of Lopez-Berestein because none of these references teach or suggest all the features of the present

claimed invention are not persuasive since as pointed out above, from the teachings of the secondary references it is evident that cholesterol has the ability to provide flexibility to the bilayer membrane of the liposomes and change the release rates and this function of cholesterol would be the same irrespective of the nature of the Phospholipid used in the formation of the bilayer membrane of the liposome.

With regard to claims 55 and 56 , the examiner points out that Lopez-Berestein teaches dieleidoyl phosphatidylcholine on col. 7, lines 66-67 and generic 'phosphatidylglycerol on col. 8, line 1 and Hersch teaches DSPG.

With regard to claims 57 and 58, Lopez-Berestein teaches DOPC and DMPC in Table 5).

REJECTION 3:

Appellant's arguments have been fully considered, but are not persuasive. Appellant argues that Hays describe(s) liposome systems that are very different than the liposomes recited in instant claims and that liposomes described by Hays would not provide liposomes with intermediate release properties. This argument is not persuasive since instant claims are composition claims and not method claims and Hays teaches the formation of liposomes using the claimed DEPC and cholesterol and Hays is further suggestive of the inclusion of a negatively charged lipid. Thus, appellant's arguments that Hays would not provide liposomes with intermediate release properties without any comparative studies are deemed to be speculative in nature. With regard to the lack of teachings of claimed ratios in Hayes, the examiner points out that Hayes teaches that

cholesterol amounts can be varied and therefore, one of ordinary skill in the art would be motivated to change its amounts thereby changing its ratio to DEPC (in claim 55). Since Hayes also suggests the inclusion of a negatively charged lipid such as phosphatidylglycerol one of ordinary skill in the art would be motivated to choose the appropriate negatively charged lipid and manipulate its amounts to obtain the best possible results particularly in view of Hayes teachings that choice of the lipid is based on the desired factors such as stability of the liposomes in blood stream (claims 56 and 58).

Appellant's arguments that Allen, Fujii or O'Rear discuss the inclusion of cholesterol within liposomes but do not teach or suggest the preparation of intermediate release liposomes are not persuasive since these references are suggestive of cholesterol function in the liposomes and that of O'Rear in particular teaches that various liposomes can be selected for the desired characteristics or manipulated to produce the desired characteristics and solute retention by liposomes and their half-life in the circulation can be controlled by appropriate manipulation of the liposomal membrane fluidity and composition. Therefore, one of ordinary skill in the art would be motivated to vary the amounts of cholesterol to obtain the desired half-life of the drug.

REJECTION 4:

Appellant's arguments have been fully considered, but are not persuasive. The examiner has already addressed appellant's arguments with regard to Hayes, Hersch, Allen, Fujii and O'Rear. Appellant argues that Anaissie does not teach or discuss

liposomes with intermediate release properties or liposomes with an elimination half-life range as described in the rejected claims and therefore does not remedy the deficiencies of Hayes alone or in combination with Hersch, Fujii, or O'Rear. These arguments are not persuasive since Anaissie is added to show the equivalency between DOPC instead of DEPC and applicant has not shown any unexpected results by substituting DEPC with DOPC.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612

Conferees:

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618